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Attorney's Docket No.: 17095CIPCON(AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Garst	Art Unit	: 1614
Serial No.	: 09/903,954	Examiner	: Fay, Zohreh
Conf. No.	: 3028		
Filed	: July 12, 2001		

Title : COMBINATIONS OF PROSTAGLANDINS AND BRIMONIDINE OR DERIVATIVES THEREOF.

Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

(1) **Real Party in Interest**

The inventor Michael Garst assigned his entire interest in this patent application to Allergan Sales, Inc. via an assignment document recorded at reel 011717, frame 0317 on November 15, 1999. Allergan Sales, Inc (now Allergan Sales, L.L.C.) is the owner of this patent application and the real party in interest in this appeal.

(2) **Related Appeals and Interferences**

There are no related appeals or interferences.

(3) **Status of Claims**

Claims 107 and 14-27 (all the currently pending claims) stand rejected.

(4) **Status of Amendments**

No amendment of any claim has been filed after the date of final rejection.

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as express mail (Label No. EL385560001US) with sufficient postage on the date indicated below and is addressed to the Box AF-Brief on Appeal, Commissioner for Patents, Washington, D.C. 20231.

10/15/2002
Date of Deposit

Bonnie Ferguson
Signature

BONNIE FERGUSON
Typed or Printed Name of Person Signing Certificate

(5) Summary of Invention

The present invention is drawn to compositions which lower intraocular pressure while providing neuroprotection to the ocular nerves and methods of preventing degeneration of the optic nerve. In its essential form the composition of the invention comprises an alpha adrenergic receptor agonist of a given structure in combination with a therapeutically effective amount of a prostaglandin. The present inventor has discovered that the combination of such agents provide a synergistic, rather than additive, therapeutic effect. In addition, this combination results in fewer side effects such as hyperemia and edema than is normally seen upon administration of a hypotensive dose of a prostaglandin. In a preferred embodiment, the alpha adrenergic agonist is brimonidine.

(6) Issues

A) Is the Invention of Claims 1-7 and 14-20 Unpatentable Pursuant to 35 USC § 103 Because the Advantages of the Claimed Compositions are Not Recited in the Claim?

B) Is the Invention of Claims 21-27 Unpatentable Pursuant to 35 USC § 103 Because the Advantages of the Claimed Compositions are Not Recited in the Claim?

(7) Grouping of Claims

The claims within each of the following sets of claims stand or fall separately from those within the other sets of claims: claims 1-7 and 14-20, and claims 21-27.

(8) Argument

A) The Invention of Claims 1-7 and 14-20 is Not Unpatentable Pursuant to 35 USC § 103, Because the Claimed Composition Is Not Obvious in View of *Searle*.

i) The Claimed Composition is not Prima Facie Obvious

In the Final Office Action mailed March 21, 2002 the Examiner rejected the pending claims as *prima facie* obvious under 35 USC §103 in view of what is alleged to be Applicant's admission on pages 2-7 of the specification and "Drug Therapy by Searle" (Searle, Janet B., *Drugs and Aging* 5:156-170(1994)). Applicants respectfully contend that the Examiner has erred in rejecting these claims in that the claimed invention is not made *prima facie* obvious in light of either reference individually or of both in combination.

To establish a *prima facie* case of obviousness, the Examiner must first provide evidence of some suggestion or motivation to modify the references or to combine the reference teachings. Second, the Examiner

must show that the person of skill in the art would have had a reasonable expectation of success if the suggestion were followed. Lastly, the prior art reference(s) must teach or suggest all the claim limitations. See e.g., Manual of Patent Examining Procedure (MPEP) § 2143.

i. The Prior Art Provides no Suggestion of the Claimed Invention

As to the first requirement, the Examiner has characterized Applicant's specification at pages 2-7 as an admission that both prostaglandins and alpha adrenergic agonists have been previously individually used for the treatment of glaucoma. To the extent that the Examiner's citation of the specification is intended to mean anything other than this, the Examiner has erred, since Applicant's specification may not be used as prior art against the currently pending claims. See e.g., *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Of course, the Searle reference (e.g., at page 157) stands for the same proposition - it discloses that alpha adrenergic agonists and prostaglandins were each under investigation for the treatment of glaucoma. There is, however, no suggestion in Searle that one could or should employ a single composition comprising a combination of such agents for the treatment of ocular hypertension.

Indeed, Searle states that among a) non-selective and relatively selective β-adrenergic agents, b) non-selective adrenergic agonists, c) miotic agents, c) selective alpha 2-adrenergic agonists and d) carbonic anhydrase inhibitors, "all of these medications have adverse effects that range from mild to severe" and "some of these medications may not be well tolerated singly or in combination." *Id.* at 157. The article goes on to indicate that newer selective alpha-2 adrenergic agonists (including brimonidine), sulphonamide-derived carbonic anhydrase inhibitors, prostaglandins, and ethacrynic acid might "be used instead of or in combination with some of the drugs currently in use". *Id.* (emphasis added). No suggestion that these drugs be used in combination with each other is made. Moreover, there is no specific suggestion that alpha adrenergic agonists should be combined with prostaglandins in a single combination for the treatment of ocular hypertension.

Searle discloses that brimonidine was effective at lowering intraocular pressure in compassionate case protocols to patients on maximally tolerated glaucoma medications. Searle concludes that brimonidine may have additive efficacy to certain other ocular hypotensive drugs. However, there is no indication of which other ocular hypotensive drugs these may be.

Searle also discloses that prostaglandins mediate inflammation in the eye, and that some of these compounds reduce intraocular pressure. In preliminary trials certain prostaglandins caused hyperemia and foreign body sensation which were of sufficient severity to preclude clinical use. While short term adverse effects of other prostaglandins, such as latanoprost were said to be relatively mild, Searle cautions that "the adverse effects of long term administration of prostaglandins are as yet unknown." *Id.* at 166. Furthermore, the article states that "the additivity of prostaglandins to other glaucoma medications is under investigation", even though it also indicates that prostaglandins would "not be expected to be additive" to certain ocular hypotensives. *Id.*

Finally Searle concludes that "[i]t has yet to be determined which of these drugs will be selected as initial glaucoma treatment . . . and which will more commonly be used secondarily as additive agents", since "[t]he additive effects of these four classes of compounds to other drugs currently used to treat glaucoma is yet to be determined. *Id.* at 167 (emphasis added).

Thus, while Searle discloses that prostaglandins and brimonidine (among other agents) appear to have efficacy as ocular hypotensives, there is no suggestion in Searle that one should combine these agents in a single composition, as is presently claimed. Indeed, Searle clearly indicates that while it may be desirable to determine if any of the surveyed agents (including carbonic anhydrase inhibitors, selective alpha 2 agonists, prostaglandins and ethacrynic acid) may be used in conjunction with other glaucoma agents, whether any of these agents may be used in a regimen with other (then-currently used) ocular hypotensive drugs "is yet to be determined", and thus unknown. Thus, Searle does not anywhere suggest that any of the surveyed agents be used with each other, much less in a single composition.

The present specification states that the administration of one or more prostaglandin in combination with one or more brimonidine derivative lowers intraocular pressure (IOP) without the accompanying inflammatory response (including hyperemia) typically found with the topical use of prostaglandins. This teaching, which provides the first real suggestion that the two agents may be administered together, is not found in Searle. Moreover, to the extent that the Examiner's citation of the Applicant's "admission" on pages 2-7 of the specification means anything other than the fact that the specification states that prostaglandins and brimonidine had been shown to have ocular hypotensive activity, Applicant respectfully contends that the current specification cannot be used as prior art against the currently pending claims. Thus, Searle does not meet the first requirement to establish a *prima facie* case of obviousness, namely providing a suggestion to modify the reference to come up with the claimed invention.

ii. The Prior Art Provides the Skilled Worker With No Reasonable Expectation of Success in Making the Claimed Invention

Searle also fails the second requirement for establishing *prima facie* obviousness; i.e., that one of skill in the art have a reasonable expectation of success in making the claimed invention. In order to have a reasonable expectation of success, there must be some degree of predictability. However, merely because Searle indicates that various agents show preliminary ocular hypotensive activity does not mean that a person of skill in the art would believe that two particular agents listed in Searle would work together well as therapeutic agents. To the contrary, Searle teaches that the adverse effects of long term administration of prostaglandins, in particular, were not then known, and that the selection of particular drugs (including prostaglandins and brimonidine) as additive agents to already approved drugs would depend in part on the incidence and severity of ocular and systemic adverse effects, which it appears had not been determined at that time. Thus, one of skill in the art would realize that there could

be no expectation of a therapeutic composition comprising a prostaglandin and a brimonidine derivative until such a determination was made.

iii. The Prior Art Does Not Provide A Teaching or Suggestion of Each Claim Limitation.

Searle also fails the third requirement for *prima facie* obviousness; that all the claim limitations be taught or suggested in the prior art. Not only is a composition comprising a combination of brimonidine and a prostaglandin not suggested in Searle, but the generic structure of claim 1 which represents brimonidine and its derivatives is completely absent from Searle in either express or implicit form. Moreover, Searle does not teach or mention the neuroprotective activity of brimonidine, which is a present as a claim limitation of claim 1, for example.

Thus, Applicant respectfully contends that the Examiner has erred in rejecting the present claims as *prima facie* obvious over Searle.

ii) The Claimed Invention Provides Unexpected Benefits Not Suggested In the Prior Art.

Even assuming *arguendo* that the present invention were to be found to be *prima facie* obvious, the Applicant respectfully submits that this finding is rebutted by the disclosure of the patent specification, which shows that the combination of a prostaglandin and a brimonidine derivative provides unique and unexpected benefits not suggested by the prior art. These unexpected results could not have been anticipated by the references cited by the Examiner, and thus the Examiner's holding that the invention of claims 1-__ is obvious is in error.

As disclosed in the present patent application, administration of one or more prostaglandin in combination with one or more brimonidine derivative lowers intraocular pressure (IOP) without the accompanying inflammatory response (including hyperemia) typically seen upon the topical use of many prostaglandins. Searle refers to examples of such adverse prostaglandin effects on page 165.

The use of a combination of a brimonidine derivative and a hypotensive prostaglandin permits the optimization of hypotensive therapeutic efficacy at a dosage of one or each of these compounds below that required for similar efficacy when only one of these compounds is used. Thus, for example, the adverse effects seen upon administration of a therapeutic dose of a prostaglandin alone can be minimized through administration of a composition containing brimonidine or a brimonidine derivative. Administration of this composition permits the same (or better) therapeutic efficacy at a lower dose of the prostaglandin.

The fact that these two compositions could be combined for the treatment of intraocular pressure without having an additive effect of adverse effects (much less with a reduction in such side effects) was surprising and totally unexpected to the Applicant.

These advantages, disclosed for the first time in the present patent specification, could not have been anticipated by the person of ordinary skill in the art at the filing date. They are not suggested by Searle. Thus, in light of such unexpected properties the invention of claims 1-___ cannot be considered obvious. See e.g., *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995). For this reason Applicants ask that the Board overrule the Examiner's holding that the claimed invention is obvious.

B) The Invention of Claims 21-27 is Not Unpatentable Pursuant to 35 USC § 103, Because the Claimed Composition Is Not Obvious in View of *Yavitz* and *Woodward*.

i) The Invention of Claim 21-27 is neither Taught nor Suggested by the Cited Prior Art.

The Examiner has rejected claims 21-27 as allegedly *prima facie* obvious over Woodward (U.S. Pat. No. 5,877,211) and Yavitz (Ocular Surg. News 17:28 (Supp. September 1999). These claims are drawn to methods for the use of brimonidine or its derivatives and a prostaglandin for the protection of the optic nerve and retinal ganglion cells in a mammal suffering from glaucoma or high intraocular pressure. Woodward is characterized as disclosing that certain prostaglandin analogs are neuroprotective, and Yavitz as disclosing that brimonidine prevents optic nerve layer thinning following LASIK laser surgery. The Examiner states that one skilled in the art would have been motivated to combine the teachings of these references "since they in combination relate to the use of the individual components as neuroprotective agents in [the] ophthalmic field." Office Action of August 29, 2001 at page 3.

However, neither cited reference suggests combining the two compounds of the present method in a single composition for the protection of retinal ganglion cells or the optic nerve. It is easy to see why this is the case; those of ordinary skill in the art are aware that the combination of glaucoma medications may in certain cases result in adverse side effects limiting their usefulness, and furthermore that any benefit of combination therapy of specific agents is unknown.

For example, as discussed above the Searle article (with which those of skill in the art must be charged with knowledge) indicates that "the additivity of prostaglandins to other glaucoma medications is under investigation", even though it also indicates that prostaglandins would "not be expected to be additive" to certain ocular hypotensives. As with the hypotensive activity of these compounds (which proceeds by different mechanisms), in light of such disclosure the person of ordinary skill in the art would

simply have no idea without further information whether the respective neuroprotective activities of brimonidine and prostglandins would be additive.

Furthermore, one of the cited references, Woodward, discloses that "ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds [prostaglandins] . . . in humans. The clinical potential of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects." Woodward at column 3, lines 27-34. In light of such disclosure, it would clearly not be obvious to the person of ordinary skill in the art that prostaglandins generally would be practically useful as a neuroprotective agent in a subject suffering from glaucoma or elevated intraocular pressure.

An invention is not obvious if the prior art merely contains an invitation to experiment. At most, in light of these two references, a person of skill in the art might wish to experiment to see whether these two agents may be used together for a combined neuroprotective effect in subjects suffering from glaucoma or elevated intraocular pressure. In light of the known inflammatory side effects of prostaglandins (see Searle et al., discussed above), it was simply unknown whether such one could combine brimonidine and a prostaglandin safely or with any added neuroprotective benefit.

The Examiner has cited In re *Kerkhoven*, 205 USPQ 1069 (CCPA 1980) in support of this rejection. *Kerkhoven* concerned a patent application drawn to methods for producing detergent compositions by the mixing of two separately dried detergents, in light of prior art disclosing the mixing of two liquid detergents, followed by a drying step, to produce the same composition. The court held that it was obvious to combine two compositions taught to be useful for the same purpose to form a third composition which is to be used for the same purpose.

The present facts are clearly different from those of *Kerkoven*. Yavitz discloses that brimonidine reduces nerve layer thinning in patients when used before and after LASIK surgery. The present claims are drawn to the use of an alpha 2 agonist of a defined structure and a prostaglandin to protect both the optic nerve and retinal ganglion cells in patients suffering from glaucoma. Thus, unlike the situation in *Kerkoven*, the prior art does not disclose that brimonidine and prostaglandins are useful for the same purpose as is now claimed.

For all these reasons, the Applicants respectfully urge the Board to reverse the Examiner's holding that claims 21-24 are obvious, and thus to permit these claims to proceed to issue.

(9) Conclusion

For the above stated reasons the Applicants respectfully request that the Examiner's finding the pending claims are obvious be overruled.

The appeal brief fee of $320.00 and the three month extension of time fee of $920.00 are to be charged to our Deposit Account No. 01-0885. Additionally, please apply any other charges or credits, to Deposit Account No. 01-0885.

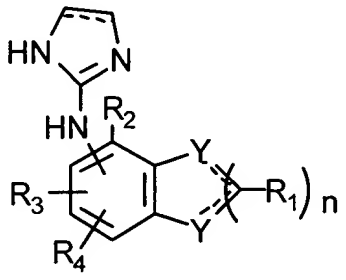
Respectfully submitted,

Date: 10/15/02

Carlos A. Fisher, Esq.
Reg. No. 36, 510

APPENDIX
Claims on Appeal

1) A topical ophthalmic composition useful for controlling elevated intraocular pressure associated with glaucoma and ocular hypertension while providing neuroprotection to the ocular nerves, comprising a combination of a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)

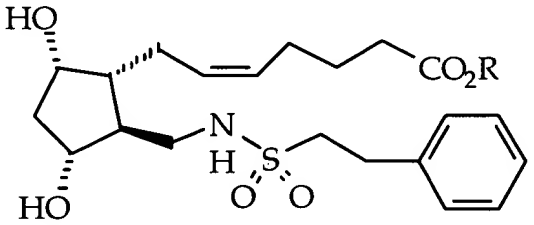


formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R_1; R_1 is hydrogen, lower alkyl or oxo; R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates a single or double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate, wherein said composition lowers intraocular pressure and provides neuroprotection.

2) The composition of claim 1 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$, PGE_2, PGE_1, prostacyclin, 15(S)-methyl-$PGF_{2\alpha}$, 16,16-dimethyl-$PGF_{2\alpha}$, 15(S)-methyl-$PGE_{2\alpha}$,16,16-dimethyl-PGE_2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-$PGF_{2\alpha}$, 18,19,20-trinor-17-phenyl-PGE_2, 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, the free acid and lower alkyl esters of $PGF_{2\alpha}$,wherein the omega chain has been replaced with phenylethylsulfonamidomethyl- , trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy $PGF_{2\alpha}$, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE_2, 11-deoxy-$PGF_{2\alpha}$, 11-deoxy-16,16-dimethyl-PGE_2, 11-deoxy-15(S)-methyl-PGE_2, 11-deoxy-15(S)-methyl-$PGF_{2\alpha}$, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

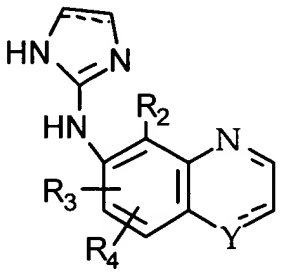
3) The composition of claim 2 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$-11-pivalyl ester, the 1-amido-15-methyl ether of $PGF_{2\alpha}$, 1-ethylamido-18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, $PGF_{2\alpha}$-1-ethyl ester, $PGF_{2\alpha}$1-isopropyl ester, the acid and isopropyl ester derivatives of $PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



R=H, i-propyl,

RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$-1-methyl ester.

4) The composition of claim 1 wherein the alpha adrenergic agent is selected from the group consisting of formula (II) wherein Y is N or O, R2 is bromine or methyl and all other variables are defined as in claim 1.

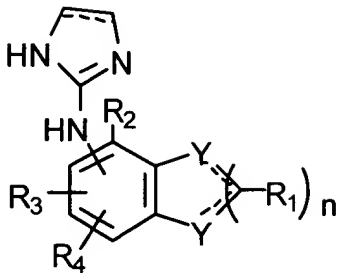


formula (II)

5) The composition of claim 3 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

6) The composition of claim 4 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

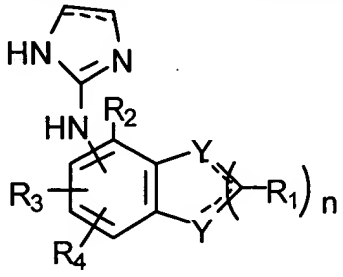
7) A method of treating a mammal suffering from glaucoma or ocular hypertension, comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)



formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R_1; R_1 is hydrogen, lower alkyl or oxo; R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates either a single or a double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

14) An article of manufacture comprising packaging material and a pharmaceutical combination comprising at least one alpha adrenergic agent and at least one prostaglandin and their pharmaceutically acceptable salts and esters as appropriate, wherein the pharmaceutical agents are effective in controlling elevated intraocular pressure associated with glaucoma and ocular hypertension and providing neuroprotection, and wherein the packaging material comprises a label which indicates that said combination can be used for control of elevated intraocular pressure or in treating glaucoma, and wherein said alpha adrenergic agent is represented by formula (I)

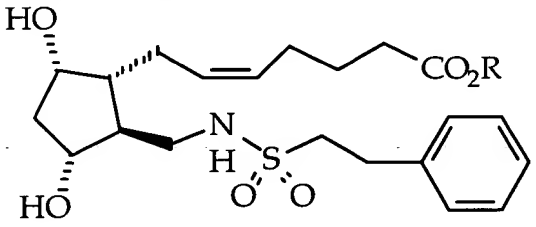


formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R_1; R_1 is hydrogen, lower alkyl or oxo; R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates a single or double bond, provided that two double bonds are not on the same carbon in the case when n=1.

15) The article of claim 14 wherein the prostaglandin is selected from the group consisting of PGF2α, PGE2, PGE1, prostacyclin, 15(S)-methyl-PGF2α, 16,16-dimethyl-PGF2α, 15(S)-methyl-PGE2a, 16,16-dimethyl-PGE2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-PGF2α, 18,19,20-trinor-17-phenyl-PGE2, 18,19,20-trinor-17-phenyl-PGF2α, the free acid and lower alkyl esters of PGF2α, wherein the omega chain has been replaced with phenylethylsulfonamidomethyl- , trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy PGF2α, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE2, 11-deoxy-PGF2α, 11-deoxy-16,16-dimethyl-PGE2, 11-deoxy-15(S)-methyl-PGE2, 11-deoxy-15(S)-methyl-PGF2α, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

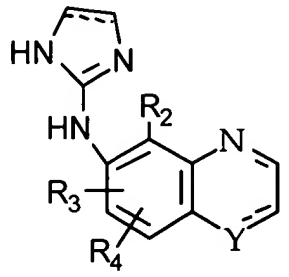
16) The article of claim 15 wherein the prostaglandin is selected from the group consisting of PGF2α-11-pivalyl ester, the 1-amido-15-methyl ether of PGF2α, 1-ethylamido-18,19,20-trinor-17-phenyl-PGF2α, PGF2α-1-ethyl ester, PGF2α1-isopropyl ester, the acid and isopropyl ester derivatives of PGF2α wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



R=H, i-propyl,

RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF2α-1-methyl ester.

17) The article of claim 14 wherein the alpha adrenergic agent is selected from the group consisting of formula (II) wherein Y is N or O, R2 is bromine or methyl and all other variables are defined as in claim 14



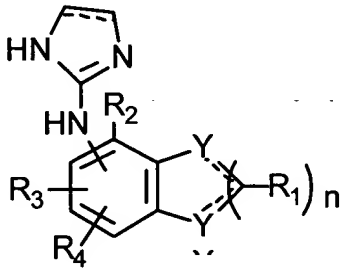
formula (II)

18) The article of claim 16 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

19) The article of claim 17 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

20) The article of claim 14 wherein the prostaglandin is the 11-pivalyl ester of PGF2α and the alpha adrenergic agent is brimonidine.

21) A method of preventing degeneration of the optic nerve and providing protection of the retinal ganglion cells of a mammal, comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)

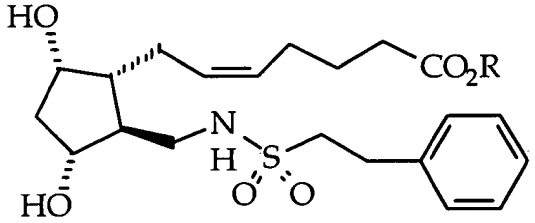


formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R_1; R_1 is hydrogen, lower alkyl or oxo; R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates either a single or a double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

22. The method of claim 21 wherein the prostaglandin is selected from the group consisting of PGF2α, PGE2, PGE1, prostacyclin, 15(S)-methyl-PGF2α, 16,16-dimethyl-PGF2α, 15(S)-methyl-PGE2a, 16,16-dimethyl-PGE2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-PGF2α, 18,19,20-trinor-17-phenyl-PGE2, 18,19,20-trinor-17-phenyl-PGF2α, the free acid and lower alkyl esters of PGF2α, wherein the omega chain has been replaced with phenylethylsulfonamidomethyl- , trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy PGF2α, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE2, 11-deoxy-PGF2α, 11-deoxy-16,16-dimethyl-PGE2, 11-deoxy-15(S)-methyl-PGE2, 11-deoxy-15(S)-methyl-PGF2α, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

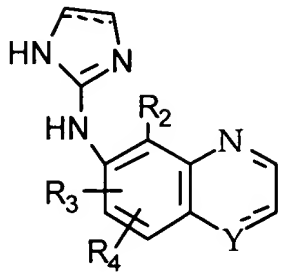
23) The method of claim 22 wherein the prostaglandin is selected from the group consisting of PGF2α-11-pivalyl ester, the 1-amido-15-methyl ether of PGF2α, 1-ethylamido-18,19,20-trinor-17-phenyl-PGF2α, PGF2α-1-ethyl ester, PGF2α1-isopropyl ester, the acid and isopropyl ester derivatives of PGF2α wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



R=H, i-propyl,

RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF2α-1-methyl ester.

24) The method of claim 21 wherein the alpha adrenergic agent is selected from the group consisting of formula (II) wherein Y is N or O, R2 is bromine or methyl and all other variables are defined as in claim 14



formula (II)

25) The method of claim 23 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

26) The article of claim 24 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

27) The article of claim 21 wherein the prostaglandin is the 11-pivalyl ester of PGF2α and the alpha adrenergic agent is brimonidine.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Garst

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Examiner: Z. Fay

Group Art Unit: Not yet assigned

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Bonnie Ferguson

ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612
Tel: 714-246-4920
Fax: 714-246-4249